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**Please find below and/or attached an Office communication concerning this application or proceeding.**

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/757,803  
Filing Date: January 14, 2004  
Appellant(s): MCSWIGGEN ET AL.

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Peter Haeberli  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 3/14/11 appealing from the Office action mailed 10/21/10.

**(1) Real Party in Interest**

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

**(2) Related Appeals and Interferences**

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

Appeal No. 2009-2562, resulting from application No. 90/008,177 (Re-examination of US Patent 7,022,828).

Appeal No. TBD, resulting from application 10/720,448, currently pending before the board.

**(3) Status of Claims**

The following is a list of claims that are rejected and pending in the application:

Claims 18-20 and 33-49 are rejected and presently pending.

**(4) Status of Amendments After Final**

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

**(5) Summary of Claimed Subject Matter**

The examiner has no comment on the summary of claimed subject matter contained in the brief.

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#### **(6) Grounds of Rejection to be Reviewed on Appeal**

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

#### **(7) Claims Appendix**

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

#### **(8) Evidence Relied Upon**

Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888)

Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000)

Matulic-Adamic et al. (US 5,998,203)

Crooke (US 5,898,031)

#### **(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

#### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 18-20 and 33-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Elbashir et al. (The EMBO Journal, 2001, Vol. 20, No. 23, pages 6877-6888), in view of Matulic-Adamic et al. (US 5,998,203), Parrish et al. (Molecular Cell, Vol. 6, pages 1077-1087, 2000), and Crooke (US 5,898,031), for the reasons of record and as explained below.

It is noted that the references are of record and cited on the PTO-892 mailed on 12/21/06.

The invention of the above claims is drawn to a chemically modified double stranded nucleic acid comprising a sense strand and an antisense strand, wherein each strand is 18 to 27 nucleotides in length, 18 to 23 nucleotides of each strand are complementary to each other, and at least 18 nucleotides of the antisense strand are complementary to a target RNA sequence, and the sense strand comprises a terminal cap moiety at the 5' and 3' end. The invention is further drawn to specific terminal cap moieties, as well as modifications to the duplex and a composition comprising the double stranded nucleic acid and a pharmaceutically acceptable carrier or diluent.

Elbashir et al. (EMBO) teach siRNAs, wherein each strand is 21-23 nucleotides in length and wherein at least 19 nucleotides of the sense strand are complementary to the antisense strand. Elbashir et al. teach chemical modification with 2'-deoxy or 2'-O-methyl modifications. Elbashir et al. teach modification of 19% of the nucleotides of a duplex 21 nucleotides in length with 2'-deoxy modifications.

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Elbashir et al. teach duplexes with 2 nt 3' overhangs, as well as blunt ended duplexes wherein all 21 nucleotides are complementary between the sense and antisense strand. Elbashir et al. teach that duplexes 21 nucleotides in length with 2 nt 3' overhangs were the most efficient triggers of sequence-specific mRNA degradation. Elbashir et al. teach duplexes wherein the sense and antisense strands are complementary at 19 or 21 nucleotide positions (see for example, Figure 1D (1<sup>st</sup> duplex) and Figure 1F (1<sup>st</sup> duplex)). Elbashir et al. teach 2'-deoxythymidine in the 3' overhang (see page 6884). The 100% modified duplex taught by Elbashir et al. is considered to not comprise ribonucleotides.

Elbashir et al. do not teach double stranded nucleic acid molecules comprising the instantly recited terminal cap moieties and do not teach 2'-deoxy-2'-fluoro or phosphorothioate modifications. Elbashir et al. do not teach a composition comprising the double stranded nucleic acid molecule and a pharmaceutically acceptable carrier.

Matulic-Adamic et al. teach chemical modifications of double stranded nucleic acid structures. The enzymatic RNA molecules of Matulic-Adamic et al. are taught to be targeted to virtually any RNA transcript and achieve efficient cleavage (see column 1) and to be sufficiently complementary to a target sequence to allow cleavage. Matulic-Adamic et al. teach the incorporation of chemical modifications at the 5' and/or 3' ends of the nucleic acids to protect the enzymatic nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules (see column 2). Matulic-Adamic et al. teach base, sugar and/or phosphate modification, as well as terminal cap moieties at

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the 5'-cap, 3'-cap, or both. Specifically, 3' phosphorothioates, inverted abasic moieties, and 2'-O-methyl modifications are utilized. Matulic-Adamic et al. teach 2'deoxy nucleotides and 2'-deoxy-2'-halogen nucleotides, wherein Br, Cl and F are representative halogens (see column 3, for example). For example, figure 3 contains a ribozyme structure that encompasses modification of at least 20%, at least 30%, at least 40% or at least 50% of the nucleotide positions, as well as the modifications instantly claimed. The modifications can be in one or both of the strands and can be modifications of different types within the same structure.

Matulic-Adamic et al. teach that preferred caps include 4', 5'-methylene nucleotides, 1-(beta-D-erythrofuransyl) nucleotides, 4'-thio nucleotides, 1,5-anhydrohexitol nucleotides, L-nucleotides, threo-pentofuransyl nucleotides, acyclic 3', 4'-seco nucleotides, 3,4-dihydroxybutyl nucleotides, 3,5-dihydroxypentyl nucleotides, 3'-3'-inverted nucleotide moieties, 3'-3'-inverted abasic moieties, 3'-2'-inverted nucleotide moieties, 3'-2'-inverted abasic moieties, 5'-5'-inverted nucleotide moieties, and 5'-5'-inverted abasic moieties (see columns 3 and 4, for example). Matulic-Adamic et al. teach compositions comprising the nucleic acid and reaction buffer, which is a diluent.

Parrish et al. teach a chemically synthesized siRNA molecule, wherein each strand is 26 bp in length. Additionally, Parrish et al. teach a 742 nt long dsRNA with extensive modification with 2'-deoxy-2'-fluoro modifications, which resulted in successful RNA interference. Parrish teaches that the 2'-deoxy-2'-fluoro modifications incorporated into the long dsRNA produces unc-22 interference and furthermore described the interference as strong (+++, see figure 5).

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Crooke teaches gapmer oligonucleotide chemistry and teaches that gapmer strategies increase oligonucleotide affinity to the target RNA (see column 9, for example). Crooke teaches chemical modifications that are incorporated to improve pharmacokinetic binding, absorption, distribution or clearance properties of the compound, affinity or specificity of the compound to target RNA, or modification of the charge of the compound (see column 7, for example).

Crooke teach that a particularly useful 2'-substituent group for increasing the binding affinity is the 2'-fluoro group (see column 12). Crooke also teaches 2'-O-methyl modifications.

It would have been obvious to synthesize a double stranded nucleic acid molecule with the structural characteristics taught by Elbashir et al., wherein the molecule is formulated in a composition with a diluent, as taught by Matulic-Adamic et al. It would have been obvious to incorporate the specific modifications taught by Parrish et al. and Matulic-Adamic et al.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), wherein the molecule is formulated in a composition with a diluent, because Matulic-Adamic et al. teach successful inhibition of target gene expression with nucleic acid molecules formulated in a diluent. Furthermore, the reactions performed by Elbashir et al. require diluents such as buffers and water.

One would have been motivated to synthesize a double stranded nucleic acid molecule, as taught by Elbashir et al. (EMBO), with the modifications taught by Parrish



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et al. and Matulic-Adamic et al. because each of the modifications were known in the art to protect nucleic acids from exonuclease degradation, which improves the overall effectiveness of the nucleic acid, as well as facilitates uptake of the nucleic acid molecules, as taught by Matulic-Adamic et al. Additionally, Parrish et al. and Matulic-Adamic et al. teach extensive chemical modification of long dsRNA and ribozymes, respectively, with successful inhibition of target gene expression.

Since Elbashir et al. (EMBO), Matulic-Adamic et al., and Parrish et al. teach modified double stranded nucleic acid molecules that inhibit target gene expression, and Crooke teaches gapmer oligonucleotide chemistry to improve pharmacokinetic properties of the oligonucleotide, one would have been motivated to synthesize duplexes, as taught by Elbashir et al., with each of the instantly recited modifications, as taught by Elbashir et al., Matulic-Adamic et al., and Parrish et al. in order to optimize the activity of the molecule, as taught by Crooke.

Additionally, antisense oligonucleotides, ribozymes, and dsRNAs are each commonly used for sequence-specific mRNA knockdown and each of these encounters delivery problems for effective application. Therefore, one would have been motivated to utilize the same modifications and techniques that have been utilized to overcome these problems with antisense oligonucleotides or ribozymes with siRNAs to add the same benefits to RNAi technology.

For example, Crooke teaches that gapmer oligonucleotide chemistry has provided antisense oligonucleotides with increased target affinity and pharmacokinetic properties. Crooke teaches that different modifications at different regions of the

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oligonucleotide have been tested in order to optimize oligonucleotide activity. Crooke teaches stepwise experimentation of modifications throughout oligonucleotides in order to find the optimal configuration. Crooke is relied upon as evidence that it is common to experiment with different known modifications at different locations to optimize oligonucleotide activity.

It would have been prima facie obvious to perform routine optimization to determine which of the known modifications or combinations of modifications are optimal. As noted in *In re Aller*, 105 USPQ 233 at 235,

More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of the specific modifications used were other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

Therefore, one would have been motivated to apply such a method to incorporate known modifications at various locations (i.e. regions/positions of duplex or pyrimidine v. purine) and amounts, as taught by Crooke, into the siRNA duplexes that were synthesized by Elbashir et al.

Finally, one would have a reasonable expectation of success given that each of the modifications were known in the art at the time the invention was made to add benefits to antisense oligonucleotides, ribozymes, dsRNAs or siRNA duplexes, as

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evidenced by Elbashir et al., Matulic-Adamic et al., Parrish et al. and Crooke, wherein each of the molecules face the same challenges, and each of which can be improved with modifications. Since Crooke teaches effectively walking modifications across antisense oligonucleotides to optimize the location of the modifications and activity of the oligonucleotide and Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach successfully synthesizing modified double stranded nucleic acid molecules, one would reasonably expect for each of the modifications to benefit the double stranded nucleic acid molecules of Elbashir et al. as well. Furthermore, the long chemically modified dsRNA taught by Parrish et al. further demonstrate that extensively modified dsRNA molecules result in RNA interference activity. Since Elbashir et al., Matulic-Adamic et al., and Parrish et al. teach modification of double stranded nucleic acid molecules and Crooke teaches experimentally determining optimal locations and levels of modification of antisense oligonucleotides, incorporating each of the modifications in the double stranded nucleic acid molecules of Elbashir et al. is considered within the realm of routine optimization.

It is noted that Elbashir et al. teach that 100% modification of one or both strands with 2'-deoxy or 2'-O-methyl modifications abolished activity. However, regardless of the results of these specific modifications at 100% of the positions of one or both strands, Elbashir et al. did modify duplexes and published data regarding successful inhibition with some duplexes and unsuccessful inhibition with others, supporting that testing of such known chemical modifications is routine in the art. The results of Elbashir et al. are considered to offer motivation to incorporate chemical modifications

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at various percentages to optimize the activity of the duplex because not all modifications result in activity at every percentage.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

### **(10) Response to Argument**

#### ***Response to Arguments--Claim Rejections - 35 USC § 103***

Applicant argues that attempts at more extensive modification beyond the 3' termini was taught to reduce the ability of siRNAs to mediate RNAi in view of the teachings of Elbashir et al. Applicant has continued to mischaracterize the teachings of Elbashir et al.

Applicant argues that Elbashir et al. teaches away from modifying more extensively than what is shown in Figure 4 because 50% and 100% modification abolished activity. Applicant continues to draw conclusions of the teachings of Elbashir et al. that are outside of the data and teachings of Elbashir et al. Elbashir et al. teaches 19% successful modification and teaches that 50% or 100% (one or both full strands) with 2'-deoxy or 2'-O-methyl (one modification only) abolished activity. Elbashir et al. does not teach any other data. Accordingly, although arguably Elbashir et al. may suggest that 100% modification of one or both strands with 2'-deoxy only or 2'-O-methyl only is less preferred, nevertheless this teaching is not commensurate to the instant

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claims which do not require 100% modification of one or both strands. None of the instant claims are identical to this teaching and therefore Elbashir et al. does not teach away from the instant claims. Although applicant continues to read the passage on page 6885 of Elbashir et al. out of context, the only “more extensive” modification that could be referred to is the complete modification of one or both strands, as from a full reading of the article is the only modification that was tested outside of the 2 or 4 nucleotides on each end.

It is noted that the interpretation of the Elbashir et al. (Tuschl) reference is argued in detail by applicant. However, the interpretation of the article has already been decided by the Board in the related appeal (Reexamination control 90/008,177, Patent 7,022,858), and the interpretation is consistent with that of the examiner in the instant rejection.

On page 27 of the decision, the board sets forth that appellant’s argument that Tuschl teaches avoiding any 2’-O-methyl modifications is unpersuasive and misstates the teachings of Tuschl. A fair reading is that more extensive 2’-deoxy or 2’-O-methyl modification beyond the two nucleotide 3’-overhang reduces the ability of siRNAs to mediate RNAi. Stating that complete substitution abolished RNAi is not the same of stating that any 2’-O-methyl modification should be avoided. It is noted that when incorporating chemical modifications into nucleic acid inhibitory molecules, it is routine to balance stability and activity. Therefore, it is a matter of routine optimization to determine an acceptable balance between a reduction in activity and an increase in stability, as long as the molecule is still in fact active.

The decision also sets forth that nucleic acid molecules are known to be degraded or hydrolyzed by nucleases *in vivo* and in culture systems and thus it is routine in the art to modify nucleic acids to resist nuclease hydrolysis, and particularly to modify with modifications that were known to enhance stability. Similarly, capping as disclosed by Matulic-Adamic et al. would be reasonably expected to sterically interfere with the active site of a nuclease (see page 25 of decision, for example).

It is well recognized in the nucleic acid inhibitor art that some types and levels of modification will yield active molecules, and some will not, thus resulting in a need for routine optimization. Applicant appears to have set forth some type of guideline requiring for every embodiment tested by Elbashir et al. to have resulted in activity. However, Elbashir et al. does teach successful modification, which would motivate one of skill in the art to incorporate modifications and test different levels of modification. The same types of chemical modifications that have been used routinely in the antisense and ribozyme art have been used in the RNAi art as well and have produced active molecules when routinely optimized.

The instant claims are not directed to any specific pattern of modification that yielded an unexpected property, but rather are directed to a very broad scope of possible modifications at varying positions depending on the target sequence, given that the claims are not directed to any specific target.

Elbashir et al. in no way teaches away from the instant claims, which are not commensurate in scope with the 100% modified duplexes that were inactive of Elbashir et al. Elbashir et al. offers motivation to incorporate modifications to reduce the cost of

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RNA synthesis and to enhance RNase resistance of siRNA duplexes (see page 6885, column 1). The fact that Elbashir et al. is silent as to modification between 19% and 100% (of one or both strands) would in fact motivate the skilled artisan to modify more extensively than the 19% to optimize the activity/stability balance.

Applicant sets forth that Elbashir et al. teaches siRNA molecules having from 9.5% to 100% modification. However, this statement is not accurate given that Elbashir et al. does not teach data covering this entire range or representative of this range in any manner. The examiner is relying strictly upon what is actually taught by Elbashir et al.

Applicant argues that the review by BPAI of Elbashir that more extensive modification beyond the 8/42 positions reduced the ability to mediate RNAi is consistent with applicant's interpretation that Elbashir et al. teaches away from further modification. This conclusion is in error given that reduction in the ability to mediate RNAi still yields molecules that are active. It is widely accepted in the nucleic acid inhibitor field that a balance is needed between stability and activity and thus a reduction in activity is often accepted to gain stability, as long as the molecule is still active. The claims do not require any specific level of activity. Applicant erroneously interprets the decision by the board as consistent with a teaching away by Elbashir et al.

The minimum required by the instant claims in fact is not far off from what was exemplified to work by Elbashir et al., given that the instant modifications can be concentrated in the terminal regions.

Applicant argues that there would not have been a reasonable expectation of success of more extensive modification in view of the teachings of Elbashir et al. It is noted that the instant claims require from 5-10 modified nucleotides on each strand, wherein each strand is 18-24 nucleotides in length. Therefore, the diminimus of the instant claims is 5 modifications per strand, one single modification more than the successful exemplification of Elbashir et al. Even when incorporating 10 modifications per strand out of a possible 24 nucleotides, some level of activity would be expected, especially if the modifications are concentrated in terminal regions.

It is noted that the instant claims are not target specific and therefore the location of the modifications completely depends upon any given target sequence. Although applicant argues that Elbashir et al. does not teach terminal caps, this is a rejection under 35 USC 103 rather than 102 and therefore it is the combination of references that renders the instant claims obvious. Terminal caps were well known in the art to protect nucleic acid molecules, as taught by Matulic-Adamic et al. This is consistent with the board decision, page 25, as set forth above.

Applicant points to *KSR International Co. v. Teleflex Inc.* (127 S. Ct. 1727 (2007)) to argue that the instant claims are directed to a new combination wherein the result cannot be predicted. As explained above, the instant claims are directed to a huge genus of modifications and combinations thereof, wherein the schematic is entirely target sequence specific. One would have been motivated to combine the prior-art elements and expect active molecules within the instant claim breadth. It is well within the grasp of the skilled artisan to select and combine known elements within the instant



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huge genus and to expect active molecules upon routine optimization of the placement of such modifications given the teachings in the nucleic acid inhibitor art. It is the routine optimization of the placement of the modifications that is relied upon for determining activity of such molecules, as it was known to perform such routine testing, as evidenced by the instant references.

In view of *KSR International Co. v. Teleflex Inc.*, when a combination of admittedly old elements produces a new and beneficial result never attained before, it is evidence of invention. However, in the instant case applicant is not claiming any specific combination or modification schematic that produces an unexpected result, but is rather claiming a huge genus of possible molecules wherein molecules within the genus are certainly considered obvious in view of the teachings of the prior art.

Applicant argues that some direction in the prior art that would provide a reasonable expectation of success is required. It is believed that the examiner has explained the teaching of the prior art and how these teachings would result in a reasonable expectation of success within the instant genus. The instant types of modifications were routinely used in the nucleic acid inhibitor art.

Applicant points to specific species within the instant genus in the instant specification and compares the molecules to those of Elbashir et al. Again, the instant genus is huge depending on the target sequence and combination/quantity of each type of the instant modifications. Applicant is pointing to species that are not representative of the instant genus and do not represent unexpected results for the instant genus.

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Armed with not only the teachings of Elbashir et al., but the combined teachings of each of the instantly cited references, the skilled artisan would have been motivated to incorporate the modification in different combinations and locations within the duplex within the instant genus and would expect to result in active molecules. The unmet need, as required by KSR, is that of balancing stability and activity with known chemical modifications.

Although applicant asserts that the instant claims require specific combinations of modifications at specific positions, the instant claims recite multiple types of modifications that can be incorporated alone or in various combinations with other modifications, rather than any one specific combination of modifications that have shown some unexpected property. Furthermore, the only positions that are specified are purines vs pyrimidines, of which there are only two choices for the skilled artisan to incorporate modifications at. The claims are not directed to any specific target sequence and therefore the incorporation at purines or pyrimidines varies depending on the specific target sequence. Therefore, each of these elements is variable rather than directed to a specific configuration as asserted by applicant.

The references collectively set forth that each of the instant types of chemical modifications were routinely incorporated into various types of inhibitory nucleic acid molecules (ribozymes, antisense, dsRNA, or siRNA molecules); that it was known to utilize the same types of chemical modifications from one nucleic acid chemistry to the other, as each faces similar delivery challenges; it was known to optimize such molecules via testing different combinations or locations of incorporation; and it was

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known to target genes in a sequence specific fashion. The modifications of Parrish et al. are specific to pyrimidines. Furthermore, as explained in the rejection under 35 USC 103(a) above, there are a finite number of choices for positions of incorporation (purine or pyrimidine).

Applicant argues that Elbashir should have taken a different approach based upon the results of Parrish if consistent with the examiner's interpretation. However, the fact that Elbashir focused on a different approach than hypothesized by applicant is irrelevant.

Furthermore, Parrish teaches extensive 2'-deoxy-2'-fluoro uridine modification with strong RNAi activity. The 2'-deoxy-2'-fluoro uridine modification represents a dsRNA that was extensively modified and acted via RNAi. There is no reason to expect that shorter dsRNAs, wherein Parrish itself teaches that duplexes 26bp in length act via RNAi, would not remain active with the same modification, particularly given that the long dsRNA of Parrish was necessarily cleaved via Dicer in the cell into short siRNA molecules in order to be loaded into RISC and be active.

There would have certainly been a reasonable expectation of activity within the instantly claimed genus of molecules given the motivation to routinely optimize siRNA molecules via balancing stability and activity wherein the molecules are readily tested and screened via routine techniques in the art. One would reasonably expect that routine optimization via adding modifications to test for stability and preservation of half life would result in active molecules when utilizing modifications that are routinely utilized to enhance the activity of nucleic acid inhibitory molecules.

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The majority of applicant's arguments appear to be upon the assumption that the instant claims are closed to a specific pattern. However, this is not the case. Although applicant asserts that a specific pattern is being claimed, the instant genus is very large, wherein applicant has not demonstrated any unexpected property of such a large genus given the motivation in the prior art to incorporate the same types of modifications, wherein the modifications would necessarily need to be incorporated into purines or pyrimidines. Each of the elements of the instant claims (modification types, purine vs. pyrimidine, and caps) are routinely optimized in the siRNA art. The specific types of modifications are commonly utilized, the only choice of position is purine vs. pyrimidine wherein the claims are not directed to any specific target, and terminal caps are routinely utilized to protect the ends of the molecule.

Applicant argues that there would not have been a reasonable expectation of success. Contrary to applicant's argument, this is not true given the instantly claimed genus. It was well within the technical grasp of the skilled artisan to combine chemical modifications that were known and routinely used to enhance stability of nucleic acid therapeutic molecules to arrive at molecules within the instantly claimed genus that would likely have activity, as it was known in the art to balance stability and activity via routinely testing different combinations/quantities of such modifications.

Applicant continues to argue the teachings of this reference via drawing their own conclusions as to results between the 19% successful modification and 100% unsuccessful modification of Elbashir et al., experiments that simply are not addressed via Elbashir. Applicant points to page 6885 of Elbashir et al. and interprets the passage

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as teaching away from producing extensively modified duplexes. This passage is interpreted by both the examiner and the board as referring to the only extensive modification that is taught by Elbashir et al., which is 100% modification. Elbashir et al. is completely silent as to modification between 8/42 positions that was successful and 100% modification of one or both strands with a single type of modification that was unsuccessful.

It is noted again that there are only two options to incorporate the instant modifications, purine or pyrimidine; wherein the quantity and location of purines or pyrimidines is entirely target sequence specific, although the instant claims are not closed to any specific target.

Applicant argues the Elbashir et al. reference again and sets forth that Elbashir attempted to stabilize molecules but failed in providing molecules that are stable and active. The basis of this argument is unfounded given that Elbashir et al. does teach active molecules that are modified. It is believed that the examiner has explained exhaustively that Elbashir et al. does not teach away from the instant claim scope in any manner, which is supported by the interpretation by the board.

Applicant argues that the instantly claimed compounds have demonstrated unexpected results. However, the data relied upon is not commensurate in scope with the instantly claimed genus, given that the instant claims embrace a huge genus resulting from many possible combinations of types of modifications at a very large genus of possible positions depending on the specific target sequence. Elbashir et al. concentrated on the terminal regions of the siRNA duplex and simply offers motivation

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to test for incorporation of modifications at other positions. Simply setting forth a duplex that yielded better results does not mean that the instant genus has an unexpected property.

**(11) Related Proceeding(s) Appendix**

Copies of the court or Board decision(s) identified in the Related Appeals and Interferences section of this examiner's answer are provided herein.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/AMY BOWMAN/

Primary Examiner, Art Unit 1635

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/Heather Calamita/  
Supervisory Patent Examiner, Art Unit 1635

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Primary Patent Examiner